Reference Values of Indices of Spontaneous Baroreceptor Reflex Sensitivity

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Spontaneous baroreceptor reflex sensitivity (BRS) is a well established method for determining baroreflex function, which can be used to assess the potential impact on survival after myocardial infarction, to detect autonomic dysfunction in diabetic patients and in human essential hypertension. The assessment of impaired spontaneous baroreflex function in individual patients contains important clinical information, but age-dependent reference values are still lacking. In the present study we evaluated spontaneous BRS in healthy human controls to determine reference values as a function of age. Two hundred and sixty-two healthy volunteers divided into six age groups (I: <20 years, f = 11, m = 9, II: 20–29 years, f = 42, m = 37, III: 30–39 years, f = 23, m = 37, IV: 40–49 years, f = 27, m = 22, V: 50–59 years, f = 19, m = 17, VI: 60–69 years, f = 5, m = 13). Electrocardiograms (ECG) and finger arterial BP were measured with each subject in the supine position (sup, 7 min) and during deep breathing (dB, 6/min, 15 cycles). BRS was assessed using the sequence technique and the alpha coefficients as obtained from a power spectrum density estimate. Due to the normal logarithmic distribution of the BRS, the limits for impaired baroreflex function at rest were defined from logarithmic data. The limits for the BRS at rest (P = .025) were calculated as (–0.0283 × age) + 2.5198 for the sequence technique. We did not find significant differences in BRS among the female and male healthy volunteers. Our analysis of the six age groups showed the expected significant decrease in BRS, which was most prominent at the transition from group III (<40 years) to group IV (<50 years). BRS at rest and during deep breathing as well as sequential and spectral BRS indices did differ significantly. The results underline the necessity of reference values to evaluate impaired baroreflex function in individual patients. Am J Hypertens 2000; 13:268–275 © 2000 American Journal of Hypertension, Ltd.

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The baroreflex is probably one of the most important cardiovascular control mechanisms adjusting heart rate (HR) and sympathetic output to the blood vessels on a beat-by-beat basis. Like many other physiologic feedback control mechanisms, baroreflex control of the HR can be modeled as a sigmoidal stimulus [systolic blood pressure (BP)]–response (R-R interval) curve with a threshold point, a saturation point, and a linear relationship inbetween.¹² The effect of a functioning baroreflex results in a dampening of systolic BP increases because of an increase of the corresponding R-R intervals and vice versa. The slope at any point of this relationship reflects the sensitivity (gain) of the...
baroreflex (i.e., the baroreceptor reflex sensitivity: BRS) in ms/mm Hg and can be used to quantitate baroreflex control of the HR.

In patients after myocardial infarction, clinical trials have shown that reduced BRS was associated with higher mortality, suggesting that BRS is an independent risk factor affecting the outcome after acute cardiovascular events.\(^3\)–\(^8\) The ATRAMI study determined BRS values below 3 ms/mm Hg as the lower limit\(^7\) using the phenylephrine method. Investigations of patients with coronary heart disease (CHD)\(^8\) have shown that unexplained low BRS values occurred mostly in CHD patients with diabetes mellitus. In patients with diabetes mellitus, BRS values were found to reflect autonomic dysfunction earlier than did conventional autonomic function tests.\(^9,\)\(^10\) Taken together, those results indicate that BRS may be used as an independent marker of autonomic cardiovascular control in different patient groups.

Many excellent experimental methods have been developed to study baroreflex physiology and pathophysiology in detail, to distinguish between different baroreceptor inputs, and to obtain the whole stimulus–response curve.\(^1,\)\(^2\) The need for intraarterial blood pressure (BP) measurement to obtain beat-by-beat values has restricted the clinical use of BRS, as have the complex and time-consuming stimuli used, such as neck suction, lower-body negative pressure, and drug bolus injections or infusions (phenylephrine, nitroprusside).\(^11\) The noninvasive assessment of BRS became possible in the mid-eighties with the Finapres (Finapres 2300, Ohmeda, Englewood, CA, USA), which measures beat-by-beat finger arterial BP using a volume clamp technique (Penaz Method). The combination of the noninvasive beat-by-beat BP measurement with the calculation of the spontaneous BRS without additional intervention increasing or decreasing the BP allowed a larger clinical use, reducing the risk and discomfort for the patient.\(^11–\)\(^15\)

Correlations among different indices of BRS including those obtained by the sequence technique, the administration of drugs affecting BP, or computation of cross-spectrum analyses of R–R and BP variability have been reported.\(^11,\)\(^12,\)\(^16\) However, although the assessment of impaired spontaneous BRS may furnish valuable clinical information, age-dependent reference values are still lacking, although several studies have documented a decrease of BRS with aging.\(^17,\)\(^18\)

The purpose of the present study was to determine age-dependent reference values of spontaneous BRS to use spontaneous BRS as an additional parameter for autonomic function tests.

### METHODS

#### Subjects

Two hundred and sixty-two healthy volunteers (female: 127, male: 135) were investigated during routine physical examinations in ambulatory rehabilitation centers. They were divided by age into six groups (group I (\(\leq\)20 years), f = 11, m = 9, group II (20–29 years), f = 42, m = 37, group III (30–39 years), f = 23, m = 37, group IV (40–49 years), f = 27, m = 22, group V (50–59 years), f = 19, m = 17, group VI (60–69 years), f = 5, m = 13). Excluding criteria were cardiovascular diseases, diseases of the respiratory system according to the medical history and based on physical examination, standard electrocardiography (ECG) and spiroergometry, any use of cardiovascular medication, and atrial or ventricular premature beats. Table 1 presents the baseline characteristics of the six groups.

#### Data Acquisition and Data Analysis

The investigations took place between 7:00 a.m. and 12:00 midnight in a quiet room with an ambient temperature ranging...
from 21°C to 25°C. The room lighting was dimmed. R-R intervals were determined from ECG recordings (Cardioscreen, Medis, Ilmenau, Germany). After 10 min of prerest, finger arterial BP of the middle finger of the right hand was measured beat-by-beat (Finapres 2300, Ohmeda, Englewood, CA, USA) during a 7-min period with the subject in the supine position, and during 150 sec of deep breathing (breathing rate 6/min). The subject’s right hand was kept at the heart level to avoid hydrostatic influences. The breathing rate was controlled during the deep breathing with the use of audio feedback and was measured with trans-thoracic bioimpedance. The biosignals were converted from analog to digital with a 12-bit resolution and sampled with 200 Hz. The data were stored on a hard disc and analyzed offline using MEDPRO software (Kohto Ltd., Moscow, Russia) on a personal computer (HP Vectra). The peak detection, artifact recognition, and statistical and spectral analyses of the time series were realized as described elsewhere. The cuff BP at the left upper arm was measured every 3 minutes using an automatic BP measurement device (Dimeq EBM 503D, Estenfeld, Germany).

Calculation of the Spontaneous BRS with the Sequence Technique The BRS values for increasing systolic BP (BRS+) and for decreasing systolic BP (BRS−) were calculated as the slope of the linear regression lines between the R-R intervals and the systolic BP values at rest (BRS+ sup, BRS− sup) and during deep breathing (BRS+ db, BRS− db). Sequences with at least three intervals, 1-mmHg BP changes, and 5-ms R-R interval changes were analyzed only if the correlation coefficients were higher than 0.7. To find the highest coefficient, systolic BP was correlated with the same R-R interval and the two following R-R intervals. The BRS was calculated as the mean value of the obtained slopes.

Calculation of the Spontaneous BRS with the Spectral Method After control for stationarity and subtraction of the mean, a sliding fast Fourier transformation of the formed time series for the R-R intervals, the measurement of systolic BP and the diastolic BP was performed as described elsewhere. The spectral resolution and the sliding step for the deep breathing and supine measurements were 7.18 mHz, 10 seconds and 3.91 mHz, 20 seconds, respectively. The power spectral densities (PSDs) were defined for the high frequency (HF, 0.15–0.4 Hz) and low frequency bands (LF, 0.04–0.15 Hz). The alpha coefficients were calculated as the square root of the mean PSD of the R-R interval spectra divided by the mean PSD of the systolic BP spectra for the two frequency bands separately. For the deep breathing, only the LF alpha coefficient was defined.

Statistics The parameter distributions were tested with the Shapiro–Wilk criteria. Group differences were tested using an analysis of variance and Scheffe’s F-test. Differences between the measurements during supine rest and deep breathing were tested with Wilcoxon’s matched pairs signed rank test. The relationship between the BRS values defined by different methods was investigated by linear regression analysis. The results are presented as mean values ± SD. Significant differences were accepted at P < .05.

RESULTS

The HR values tended to be higher and the BP values tended to be lower in the females compared with the males. The body mass index and BP values did not differ significantly between any of the age groups in our study, which indicates comparable baseline values of the subjects at supine rest. It also underlines the physical fitness of the investigated elderly subjects.

The BRS values were similar in the female and male subjects. Table 2 presents the male and female BRS+ sup results for all age groups as an example. Consequently, the further BRS analysis did not show significant differences between the female and male subjects.

Our analysis of the six age groups showed the expected significant decrease in BRS with age, which was most prominent at the transition from age group III (30–39 years) to age group IV (40–49 years). Figure 1 presents the age-dependent changes in the parameter BRS+ sup as a box plot.

Table 3 summarizes the BRS results for all age groups. Despite the significant correlation between BRS values (minimum 0.644, BRS LF db vs BRS+ sup; maximum 0.895, BRS+ sup vs BRS− sup), the BRS at supine rest and deep breathing as well as the BRS indices calculated using the sequence technique and spectral analysis did differ significantly. In addition,
the BRS values for increasing systolic BP were higher than those for decreasing BP during the deep breathing, and the spectral indices of BRS in the HF band tended to be higher than the BRS indices calculated for the LF band at supine rest. The increase of BRS with deep breathing and the differences of BRS values for increasing systolic BP compared with BRS for decreasing BP showed the tendency to be attenuated with age.

Because of the normal logarithmic distribution of the BRS, the limits for impaired baroreflex function were defined from logarithmic data. Figure 2 shows the confidence limits as a function of age for the pa-

The results are expressed as mean ± SD. BRS+ sup, BRS calculated using the sequence technique for increasing systolic BP during supine rest; BRS− sup, BRS calculated using the sequence technique for decreasing systolic BP during supine rest; BRS+ db, BRS calculated using the sequence technique for increasing systolic BP during deep breathing; BRS− db, BRS calculated using the sequence technique for decreasing systolic BP during deep breathing; BRS LF sup, spectral BRS for the LF band during supine rest; BRS LF db, spectral BRS for the LF band during deep breathing; BRS HF sup, spectral BRS for the HF band during supine rest. # Significant group difference vs. group I. * Significant group difference vs. group II. § Significant group difference vs. group III. (Analysis of variance, Scheffé F-test, P < .05.)
DISCUSSION

As to the effects of aging, our results are in keeping with previous published data.11,16–18,21,22 Furthermore, the BRS limit of 3 ms/mmHg,7 known from the ATRAMI study, is comparable to the lower limits for the age groups IV–VI of our study. The lower limits for patients <40 years are considerably higher, a finding that needs to be considered when investigating younger populations.

Kim et al.22 described results for a group of normal male volunteers (n = 33, age 38 ± 16 years, nonsmokers), and found BRS values during rest of 14.3 ± 6.5 ms/mmHg and spectral BRS (coherence spectra in the LF band) of 13.7 ± 6.7 ms/mmHg, which were comparable to BRS in our present age group III with 15 ± 8 ms/mmHg for the sequence technique and 11 ± 5 ms/mmHg for the spectral method. Those authors did not find significant differences between the methods for BRS calculation using the sequence technique, spectral analysis, and complex demodulation. The correlation coefficients between methods were higher than those in the present study. Possible reasons for the lower correlation coefficients and the significant differences between methods in our study might be the use of separate fast Fourier transformation of the time series without checking the coherence values in the frequency bands. The relatively short recording time of 7 min might also be responsible for statistical inconsistencies. In addition the correlation criteria used for the sequence technique by Kim et al. (correlation coefficient >0.9) were stronger than in our study. Kim et al. did not analyze the HF band, because direct influences of respiration on the sinus node and the modulation of vagal tone make it difficult to differentiate between baroreflex responses and other influences.22

Smyth et al.20 excluded inspiratory R-R intervals from their analysis when describing the Oxford method, because of the reduced correlation with systolic BP values. They also showed the lack of correlation shortly after the appearance of K-complexes in the electroencephalogram, which might illustrate the importance of central autonomic tone and the influence of arousal stimuli to baroreflex function.

Especially during deep breathing, spontaneous baroreflex function is modified by the respiratory gating of baroreceptor stimulation of vagal motoneu-
rions, showing inspiratory suppression and expiratory facilitation of autonomic outflow, but with electrical stimulation of the carotid sinus nerve in humans, the vagal reflex response during inspiration did not differ from the expiratory response. Despite these influences, which might be the reason for the differences of BRS values at supine rest and deep breathing as well as between the alpha coefficients in the LF and HF bands, the BRS HF values were significantly correlated with the other BRS values in our study. We did not differentiate between inspiratory and expiratory responses.

Based on our experience and as described elsewhere, a reduced baroreflex function is sometimes visible in the time series of the systolic and diastolic BP, showing more pronounced fluctuations. In the present study, the enhancement of the respiratory component of the PSD of diastolic BP was often a sign for low BRS values, illustrating the lack of dampening influence of the baroreflex.

A problem in using spectral methods is the non-stable presence of spectral peaks in the LF frequency band and the window width of 256 sec, which is too large to detect those dynamic changes in the frequency of Mayer waves. Animal studies of rhythmic activity of autonomic neurons controlling blood vessel diameter and cardiac performance (heart rate and contractility) have shown that the frequency of Traube-Hering waves (respiratory waves) and Mayer waves (slower than Traube-Hering waves) as well as the peak-to-peak amplitude of the systemic arterial BP can change at rest tremendously. The frequency of Mayer waves can vary between 1 and 5 cycles per minute, which can make it difficult to describe them precisely using fixed frequency band limits (0.04–0.15 Hz). Model studies of BRS have also shown that the BRS gain is frequency dependent, showing increases in gain with decreasing frequencies of systolic BP oscillations.

The analysis of short sequences such as those performed with the sequence technique or with complex demodulation might be more suitable to assess dynamic changes in spontaneous BRS, which can cause coefficients of variation of about 50%. This also allows the separate analysis of sequences with an effective baroreflex only.

According to our results, it is necessary to establish reference values for the method used to detect reduced baroreflex sensitivity in individual patients. The defined confidence limits for spontaneous BRS during supine rest when using the sequence technique can be helpful in avoiding misinterpretation due to the influence of aging as well as during long-term follow-up studies.

LIMITATIONS OF THE METHODOLOGY USED

Spontaneous BRS represents only a part of the complex neural and humoral mechanisms controlling cardiovascular function. The activation of sympathetic afferents, changes in central integration, interference with other efferent activities, and different target organ responses may directly affect BRS. Thus, it is not surprising that BRS may differ according to different methodologies used to calculate the slope of the regression line relating BP changes to concomitant R-R interval modifications.

In fact, the spontaneous BRS values differ from the BRS values obtained in the classic way (intraarterial BP measurements and pharmacological tests using phenylephrine and nitroprusside). Comparison studies have shown that the spontaneous BRS is closely correlated with the drug-induced BRS methods during resting conditions with low levels of external or internal stimulation. Parlow et al. showed a high correlation with the slopes obtained during phenylephrine and nitroprusside infusions using the tangent method applied to the resting preinjection BP values.

The conditions met at the preinjection systolic BP level might be the most likely for the individual spontaneous BRS at rest, which can be inhibited or overridden during responses to excessive stimuli as well as by changes in central vagal and sympathetic tone. Drug-induced changes of mean arterial pressure move the operating point into a different range, which may result in different gains. Therefore spontaneous BRS measures baroreflex sensitivity according to the actual operating point at the response curve, which depends on the BP level and the current functional state. Consequently, a single short-term measurement of spontaneous BRS must be interpreted with caution, considering that the exact position of the operating point on the whole stimulus–response curve is not known.

Other possible causes for disturbed or unreliable spontaneous BRS measurements are most often premature beats, especially in patients. Frequent supraventricular premature beats and ventricular premature beats disturb BRS measurements independent of how arterial BP is measured or which test for BRS measurements is used. Consequently, the editing of the ECG by an experienced observer and the use of sufficient artifact removal algorithms are absolutely necessary. The usually more pronounced changes of systolic BP during deep breathing and increase in heart rate variability could be helpful in patients and healthy subjects with very low systolic BP changes at supine rest, but might also cause the confluence of Traube-Hering waves with Mayer waves and/or influence the sinus node directly and/or change central...
sympathetic and vagal tone. It needs also to be considered that respiratory sinus arrhythmia is not due simply to baroreflex-mediated changes of vagal outflow alone\textsuperscript{23} and that respiratory driven BP-HR coupling might mask the reflex changes of HR to spontaneous BP changes, because of the mentioned gating mechanism.

The amount of spontaneous changes in systolic BP is a limiting factor for spontaneous BRS measurements. Additional tests are necessary, if the occurring changes in systolic BP are not high enough or the operating point is close to the threshold or saturation level of the baroreflex. The different mathematical algorithms used to define spontaneous BRS seem to be comparable and all have advantages and limitations. Described methods include regression analysis\textsuperscript{1,2,3,6,9–16,20} spectral and cross-spectral analysis\textsuperscript{1,2,3,6,9,14,18,21,22,25,28} calculation of transfer functions or impulse response function\textsuperscript{29,30} and complex demodulation\textsuperscript{22} as well as chaos theory.\textsuperscript{31} Kim et al. obtained nearly identical mean BRS values using three different algorithms for a group of 33 male volunteers.\textsuperscript{22}

Of primary importance to us is that the method used for clinical screening should be fast, reliable, and easy to use. We assume that to detect complete cardiac denervation, a deep breathing test or an elaborate check of the supine resting HR dynamics is already sufficient, which underlines the importance and clinical relevance of the already used standardized clinical autonomic function tests,\textsuperscript{32–35} including the comparison with age reference values.

The quantification of heart rate variability and baroreflex sensitivity in combination with different tests enhancing cardiac vagal nerve traffic or sympathetic nerve activity can give deeper insight into the individual pattern of regulation, which might allow the early detection of autonomic dysfunction at a time when intervention is still possible. While accepting the limits of the methodology, spontaneous BRS can be used as an early indicator. Consequently, it can also be used for evaluating and adjusting therapeutic management.\textsuperscript{33–35}

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**REFERENCES**


